

Drug Class Review

Targeted Immune Modulators

Final Report Update 2
Executive Summary

November 2009



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The literature on this topic is scanned periodically.

This report reviews information about the comparative effectiveness and safety of drugs within a pharmaceutical class. The report is neither a usage guideline nor an endorsement or recommendation of any drug, use, or approach. Oregon Health & Science University does not endorse any guideline or recommendation developed by users of this report.

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INTRODUCTION

Targeted immune modulators, commonly referred to as biological response modifiers or simply *biologics*, are a relatively new category of medications used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ulcerative colitis. The US Food and Drug Administration approved the first of the biologics (infliximab) in 1998 and approved 9 additional agents since that time for treating various rheumatic conditions and plaque psoriasis: etanercept (1998), anakinra (2001), adalimumab (2002), alefacept (2003), efalizumab (2003), abatacept (2005), rituximab (2006), natalizumab (2008), and certolizumab pegol (2008). Table 1 summarizes currently approved biologics in the United States, including trade name, manufacturer, route of administration, therapeutic mechanism of action, and approved (labeled) uses.

Table 1. Targeted immune modulators

Generic name	United States trade name	Manufacturer	Route	Half-life	Onset of action	Mechanism of action	Labeled uses
Abatacept	Orencia®	Bristol Myers Squibb	Intravenous	8-25 days	>12 days	CTLA 4-Ig	RA JIA
Adalimumab	Humira®	Abbott	Subcutaneous	10-20 days	1-14 days	TNF inhibitor	RA JIA PsA AS Crohn's disease Plaque psoriasis
Alefacept	Amevive®	Astellas	Intramuscular	11-12 days	30-60 days	CD2 antagonist	Plaque psoriasis
Anakinra	Kineret®	Amgen	Subcutaneous	7-8 hours	7-21 days	IL-1 receptor antagonist	RA
Certolizumab pegol	Cimzia®	UCB, Inc	Subcutaneous	14 days	2-4 weeks	TNF inhibitor	RA Crohn's Disease
Efalizumab ^a	Raptiva®	Genentech	Subcutaneous	6.2 days	14 days	CD11a inhibitor	Plaque Psoriasis
Etanercept	Enbrel®	Amgen Wyeth Immunex	Subcutaneous	4.3 days	1-28 days	TNF inhibitor	RA JIA PsA AS Plaque psoriasis
Infliximab	Remicade®	Centocor	Intravenous	9.8 days	2-14 days	TNF inhibitor	RA Crohn's disease PsA AS Ulcerative colitis Plaque psoriasis
Natalizumab	Tysabri®	Biogen-Idec	Intravenous	7-15 days	2-4 weeks	Anti-IgG4	Crohn's disease
Rituximab	Rituxan®	Genentech IDEC	Intravenous	19 days	30-60 days ^b	Anti-CD 20a	RA

AS, ankylosing spondylitis; IgG, immunoglobulin G; IL, interleukin; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

^a This drug was voluntarily withdrawn from the market since June 2009.

^b American College of Rheumatology 20 response at 56 days in product labeling.

Scope and Key Questions

The purpose of this report is to review the comparative effectiveness, safety, and tolerability of targeted immune modulators in the treatment of adult patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis, and pediatric patients with juvenile idiopathic arthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

The participating organizations approved the following key questions to guide the review for this report:

1. How do included drugs compare in their efficacy and long-term effectiveness for alleviating symptoms and stabilizing the disease in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis?
2. What are the comparative incidence and severity of complications associated with the use of these drugs?
3. Do the included drugs differ in effectiveness or adverse events in different age, sex, or ethnic groups, or in patients taking other commonly prescribed drugs?

METHODS

Literature Search

To identify articles relevant to each key question we searched MEDLINE, Embase, The Cochrane Library, and the International Pharmaceutical Abstracts; we used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications (rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, plaque psoriasis), drug interactions, and adverse events with a list of 10 specific targeted immune modulators (abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, efalizumab, etanercept, infliximab, natalizumab, rituximab). We limited the electronic searches to "human" and "English language"; we searched sources from 1980 to 2009 (April) to delimit literature relevant to the scope of our topic.

We used the National Library of Medicine publication type tags to identify reviews, randomized controlled trials, and meta-analyses; we also manually searched reference lists of pertinent review articles and letters to the editor. Additionally, we hand-searched the Center for Drug Evaluation and Research database to identify unpublished research submitted to the US Food and Drug Administration.

Further, the Center for Evidence-based Policy at the Oregon Health and Science University contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations, using a protocol available at www.ohsu.edu/drugeffectiveness. We received dossiers from 8 pharmaceutical companies (Abbott Laboratories, Amgen Pharmaceuticals,

Astellas Pharmaceuticals, Biogen, Bristol Myers Squibb, Centocor, Genentech, UCB Inc., and Wyeth/Amgen Pharmaceuticals).

Validity Assessment

We assessed the internal validity (quality) of trials based on predefined criteria developed by the United States Preventive Services Task Force (ratings: good-fair-poor) and the National Health Service Centre for Reviews and Dissemination. External validity (generalizability) was assessed and reported but did not influence quality ratings. We did not rate the quality of pooled data-analyses.

Trials that had a fatal flaw in 1 or more categories were rated poor quality and not included in the analysis of the evidence report; trials that met all criteria were rated good quality. The majority of trials received a quality rating of fair. This includes studies that presumably fulfilled all quality criteria but did not report their methods to an extent that answered all of our questions. Therefore, the “fair quality” category includes trials with quite different strengths and weaknesses and a range of validity.

RESULTS

Our conclusions are based on the review of 3451 abstracts and the inclusion of 237 studies. The large majority of these studies was funded by the pharmaceutical industry and could be classified as efficacy trials with highly selected patients. Few studies existed that enrolled less selected, primary care based populations. Overall, however, results between efficacy trials and more generalizable effectiveness studies appear to be consistent with only small variations in the magnitude of effects.

In summary, insufficient evidence exists for most comparisons about the efficacy, effectiveness, and safety of abatacept, adalimumab, alefacept, anakinra, certolizumab, etanercept, infliximab, natalizumab, and rituximab for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, and plaque psoriasis.

The most obvious differences that might be clinically decisive for choosing a targeted immune modulator involve dosage and administration. Abatacept, infliximab, natalizumab, and rituximab require intravenous administration at different intervals and present the danger of rare but severe infusion reactions. Adalimumab, anakinra, certolizumab, and etanercept can be administered subcutaneously by the patient. Alefacept requires an intramuscular injection. Furthermore, administration intervals differ substantially: adalimumab requires an injection once a week or once every other week, anakinra has to be administered daily, and etanercept and certolizumab every week or every other week.

Key Question 1. Comparative Effectiveness

Rheumatoid Arthritis

One fair quality, double-blinded head-to head trial provided evidence of moderate strength that abatacept and infliximab do not differ in efficacy for the treatment of rheumatoid arthritis up to 6

months. The safety profile, however, appeared to be better for abatacept than for infliximab with fewer serious adverse events (9.6% compared with 18.2%) and fewer serious infections (1.9% compared with 8.5%).

Other direct comparisons of targeted immune modulators for the treatment of rheumatoid arthritis are limited to one small randomized-controlled trial and multiple observational studies rendering evidence of low strength. These studies indicated no differences in efficacy and safety between adalimumab and etanercept but greater response rates for adalimumab and etanercept compared with infliximab. No differences in safety were obvious in these studies. All of the observational studies were population-based and have high applicability.

None of these studies provided any evidence on radiographic outcomes.

Adjusted indirect comparisons suggested greater efficacy for adalimumab, etanercept, and infliximab compared with anakinra for the treatment of rheumatoid arthritis.

The general efficacy of abatacept, adalimumab, anakinra, certolizumab, etanercept, infliximab, and rituximab for the treatment of rheumatoid arthritis was well established by multiple good to fair randomized-controlled trials and meta-analyses. Effect sizes were large and consistent across studies.

Juvenile Idiopathic Arthritis

No head-to-head trial comparing the efficacy and safety of targeted immune modulators for the treatment juvenile idiopathic arthritis were available. The general efficacy of abatacept, adalimumab, etanercept, and infliximab for the treatment of juvenile idiopathic arthritis was supported by one randomized-controlled trial for each drug. Sample sizes of these studies, however, were small (overall data on only 369 patients) and active run-in periods limited the applicability of results. In efficacy trials significantly fewer patients on targeted immune modulators (20% to 37%) experienced disease flares than children treated with placebo (53% to 81%).

Ankylosing Spondylitis

No head-to-head trials provided direct evidence on the comparative efficacy of biologics for ankylosing spondylitis. One study conducted indirect comparisons and summarized the comparative efficacy quantitatively. The authors reported no significant differences in treatment response among adalimumab, etanercept, and infliximab. The general efficacy of adalimumab, etanercept, and infliximab for the treatment of moderate to severe ankylosing spondylitis was supported by several good to fair randomized-controlled trials and one meta-analysis. In efficacy trials 57% to 80% of patients treated with targeted immune modulators achieved an ASAS20, compared with 20% to 30% of patients on placebo.

No studies on the efficacy and safety of targeted immune modulators for the treatment of ankylosing spondylitis in children are available.

Psoriatic Arthritis

No head-to-head trials provided evidence on the comparative efficacy of biologics for psoriatic arthritis. One study conducted indirect comparisons and summarized the comparative efficacy quantitatively. The authors reported no significant differences between adalimumab, etanercept,

and infliximab. The general efficacy of adalimumab, alefacept, etanercept, and infliximab for the treatment of active psoriatic arthritis was supported by several good to fair randomized-controlled trials and one meta-analysis. In efficacy trials 39% to 50% of patients treated with targeted immune modulator drugs approved by the US Food and Drug Administration achieved an ACR50, compared with 0% to 10% of patients on placebo.

No studies on the efficacy and safety of targeted immune modulators for the treatment of psoriatic arthritis in children are available.

Crohn's Disease

No head-to-head trials provided evidence on the comparative efficacy of biologics for Crohn's disease. The general efficacy of adalimumab, certolizumab, infliximab and natalizumab for the treatment of moderate to severe Crohn's disease was supported by several good to fair randomized-controlled trials and meta-analyses. In efficacy trials 26% to 57% of patients treated with targeted immune modulators achieved a CDAI remission (CDAI <150), compared with 12% to 30% of patients on placebo.

The only study in a pediatric population with Crohn's disease was a dose ranging study without placebo arm that did not meet our eligibility criteria. In the active run-in phase (10 weeks) 88% of children achieved remission.

Ulcerative Colitis

No head-to-head trials provided evidence on the comparative efficacy of biologics for ulcerative colitis. There were two poor trials that provided limited information on general efficacy but were rated poor quality due to high attrition and other factors such as concerns about blinding. In these poor efficacy trials 25% to 35% of patients treated with targeted immune modulators achieved clinical remission from ulcerative colitis, compared with 10% to 16% of patients on placebo.

No studies on the efficacy and safety of targeted immune modulators for the treatment of ulcerative colitis in children are available.

Plaque Psoriasis

No head-to-head trials provided evidence on the comparative efficacy of biologics for plaque psoriasis. One study conducted indirect comparisons and summarized the comparative efficacy quantitatively. The authors reported no significant differences in response to treatment among alefacept, etanercept, and infliximab. The general efficacy of adalimumab, alefacept, etanercept, and infliximab for the treatment of moderate to severe plaque psoriasis was supported by several good to fair randomized-controlled trials and two meta-analyses. In efficacy trials 50% to 80% of patients treated with targeted immune modulators achieved a PASI 75 response, compared with 5% to 20% of patients on placebo.

One study assessed the efficacy of etanercept for plaque psoriasis in children and adolescents. Significantly more children in the etanercept group than in the placebo group experienced a response.

Key Question 2. Comparative safety

The evidence on the comparative safety of targeted immune modulators was sparse. One randomized-controlled trial provided moderate strength evidence that infliximab leads to higher rates of serious adverse events (18.2% compared with 9.6%) and serious infections (8.5% compared with 1.9%) than abatacept.

Based on one non-randomized trial and one prospective cohort study rendering evidence of low strength, no differences in adverse events between etanercept and infliximab could be detected.

The combination of two targeted immune modulators substantially increased the frequency of serious adverse events (15% compared with 3%) without any additional yield in benefits.

Regarding the general tolerability and safety, in placebo-controlled efficacy studies targeted immune modulators generally appeared to have a good tolerability profile, although some rare but serious adverse events such as serious infections, lymphoma, leucopenia, malignancies, or demyelinations are of concern for all targeted immune modulators. The evidence, however, is currently insufficient to draw any conclusions about the comparative risk for serious adverse events.

Injection site or infusion reactions, abdominal pain, nausea, headache, diarrhea, upper respiratory tract infections, and urinary tract infections were the most commonly reported adverse events. More than 90% of patients in efficacy trials experienced at least one adverse event. Incidence rates of injection site reactions appeared to be significantly higher with anakinra than with anti-TNF drugs (67% compared with 16% to 22% for other subcutaneous targeted immune modulators). Rituximab appeared to have the highest rate of infusion reactions (77% compared with 9% to 17% for other intravenous targeted immune modulators), some of which were fatal.

Discontinuation rates because of adverse events in patients treated with targeted immune modulators ranged from 3% to 20% and generally did not differ significantly from those in patients treated with placebo.

For newer targeted immune modulators such as abatacept, certolizumab, natalizumab, or rituximab long-term safety data are generally missing.

Key Question 3. Subgroups

The overall grade of the evidence on efficacy and tolerability in subgroups was low. We did not identify any study specifically designed to compare the effect of targeted immune modulators in one subgroup of patients compared to another. Subgroup analyses and indirect evidence from placebo-controlled trials provided evidence for some drugs.

Indirect evidence exists from two pooled analyses and a retrospective cohort that age is not associated with greater clinical response rates or safety in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. In contrast to this, a separate study found the response to treatment with etanercept and infliximab for rheumatoid arthritis was better in patients younger than 65 years. No differences in adverse events between patients with ankylosing spondylitis, rheumatoid arthritis, and psoriatic arthritis older than 65 years and those younger were reported, with the exception of bacterial pneumonia, which was more common in older patients in their 70's than those in their 50's. The same report also showed that bacterial

pneumonia was more common in women than men and those with respiratory conditions when treated with infliximab.

Evidence was mixed whether patients with congestive heart failure have a higher risk of hospitalization and mortality when treated with etanercept and infliximab. Additionally there is low evidence to show that commonly prescribed concomitant medications such as statins or antihypertensives appear to have little or no increase in adverse events.

SUMMARY

The main findings of this review are summarized in Table 2.

Table 2. Summary of the evidence by key question

Key question	Strength of evidence	Conclusion
1. Comparative efficacy for rheumatoid arthritis	Moderate	Based on 1 randomized controlled trial, no difference in efficacy between <i>abatacept</i> and infliximab
	Low	Based on indirect comparisons and 1 observational study, no difference in effectiveness between adalimumab and etanercept
	Insufficient	Based on indirect comparisons and 1 observational study, conflicting evidence on the comparative effectiveness of adalimumab and infliximab
	Moderate	Based on 2 trials and 4 observational studies, greater effectiveness of etanercept than infliximab
	Low	Based on indirect comparisons, greater effectiveness of adalimumab, etanercept, and infliximab compared with anakinra
	Insufficient	No evidence available for all other comparisons
1. Comparative effectiveness for juvenile idiopathic arthritis	Insufficient	No comparative evidence available
1. Comparative effectiveness for ankylosing spondylitis	Low	Based on indirect comparisons, no difference in effectiveness between adalimumab, etanercept and/or infliximab
1. Comparative effectiveness for psoriatic arthritis	Low	Based on indirect comparisons, no difference in effectiveness between adalimumab, etanercept and/or infliximab
1. Comparative effectiveness for Crohn's disease	Insufficient	No comparative evidence available
1. Comparative effectiveness for ulcerative colitis	Insufficient	No comparative evidence available
1. Comparative effectiveness	Insufficient	No comparative evidence available

Key question	Strength of evidence	Conclusion
for plaque psoriasis		
2. Comparative safety	Moderate	Based on 1 randomized controlled trial, higher rates of serious adverse events and serious infections for infliximab than for abatacept
	Low	Based on 1 trial and 1 observational study, no differences between etanercept and infliximab
	Insufficient	No evidence available for all other comparisons
	High	Based on 2 randomized controlled trials, substantially higher rates of serious adverse events for combination therapies of anakinra with etanercept and abatacept with etanercept than for monotherapies
3. Subgroups - age	Insufficient	The evidence on the effect of age is contradicting and insufficient to draw conclusions
3. Subgroups - sex	Insufficient	The evidence is mixed and insufficient to draw conclusions
3. Subgroups - ethnicity	Insufficient	The evidence is mixed and insufficient to draw conclusions
3. Subgroups - comorbidities	Insufficient	The evidence is mixed and insufficient to draw conclusions